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Diffusing Capacity, Specific Diffusing Capacity and Interpretation of Diffusion Defects

LARRY N. AYERS, MD, *Oklahoma City,*
MARVIN L. GINSBERG, MD, JERRY FEIN, MD, *and* KARLMAN WASSERMAN, MD, PhD,
Torrance, California

Six pathophysiologic mechanisms of a reduced single breath CO diffusing capacity are discussed and the usefulness of relating carbon monoxide (CO) uptake to the functioning alveolar volume (DL/VA, specific diffusing capacity) is illustrated for several pulmonary diseases. In patients with emphysema and pulmonary emboli (pulmonary vascular occlusive disease), reduced CO uptake is associated with significantly reduced DL/VA and is compatible with reduction of pulmonary capillary bed. In patients with pulmonary alveolar proteinosis, improvement in CO uptake and DL/VA follows lung lavage and suggests that lung units partially filled with proteinaceous material are responsible for hypoxemia, reduced CO uptake and reduced DL/VA. In most cases of radiation fibrosis, sarcoidosis and miscellaneous interstitial fibrosis, reduced CO uptake is associated with a normal DL/VA and suggests that loss of alveolar units, both capillaries and alveoli, has occurred. New regression equations for DL and DL/VA are established for children and adults. DL/VA is linearly related to height and independent of age and sex, while different predictive equations must be used for DL for the 5 through 17 and 18 through 76 age groups. The new regression equations for DL show better correlation in adults we studied over 50 years of age than previous regression equations which use a constant reduction of 2 to 3 ml CO per minute per mm of mercury for each 10 years of adult aging.

From the Respiratory Disease Division, Harbor General Hospital, Torrance, California and University of California, Los Angeles, School of Medicine.

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Reprint requests to: Larry N. Ayers, MD, Pulmonary Disease Section, Department of Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, OK 73104.

ABBREVIATIONS USED IN TEXT

A-a = alveolar-arterial
DL = diffusing capacity of the lung for carbon monoxide
DL/VA = rate of carbon monoxide transfer per unit of alveolar volume (specific diffusing capacity)
VA = alveolar volume

THE PRIMARY FUNCTION of the lungs is to arterialize mixed venous blood. This is accomplished by exposure of blood in the lung capillaries to the alveolar air, a derivative of the gas exchange between the capillary blood and inspired air. In order to transfer oxygen molecules from atmospheric air to blood, the inspired air must enrich the oxygen in the alveolar gas to raise its partial pressure to levels above that in the blood entering the lungs. The transfer process entails diffusion of oxygen molecules across the alveolar-capillary membrane through the plasma into the red cell where it combines with hemoglobin. The rate of diffusion depends on (1) the difference between the partial pressure of the oxygen in the alveolus and the red cell, (2) the distance between the gas phase in the lungs and the red cell, (3) the gas exchange surface area and (4) the solubility of oxygen in lung tissue and plasma.

Therefore, the lungs' capacity to transfer oxygen from the inspired gas to the blood can be reduced due to (1) failure of the inspired gas to reach alveoli (poor distribution of ventilation), (2) loss of alveoli as a result of fibrosis and scarring of the entire gas exchange unit or lung resection, (3) enlarged alveolar spaces with reduction in gas exchange surface (emphysema), (4) a deficiency in red blood cells increasing the intravascular diffusion distance (anemia or abnormal hemoglobin), (5) loss of pulmonary capillary bed (thromboembolism or vasculitis) and (6) increase of the distance between the gas and blood phase of the functional lung unit due to filling of the alveoli by pathological material or thickening of the alveolar-capillary membrane resulting from interstitial fibrosis, inflammation or edema.

Today, carbon monoxide—a gas that has a much greater affinity for hemoglobin than oxygen, yet similar solubility characteristics—is the most frequently used test gas for measuring the diffusing capacity of the lungs.[1,2,5,9-12,15,16,18,20-22]

We have found that we could obtain more useful information from the single breath carbon monoxide (CO) diffusing capacity measurement by differentiating the six pathophysiological states described above and illustrated in Figure 1, all of which might cause a reduction in the transfer of CO as well as oxygen. It would be incorrect to equate all reductions in CO uptake rate to alveolar-capillary membrane thickening or a diffusion abnormality, an interpretation commonly made. Differentiation between the various factors which can cause a reduction in CO uptake rate is facilitated by the simultaneous measurement of the alveolar volume (VA) in which the CO is diluted and from which the CO might be absorbed.[11,19] Thus, the rate of CO transfer per unit of alveolar volume (specific CO diffusing capacity) might provide additional information regarding the pathophysiology of disease which results in a reduced diffusing capacity measurement. When one uses this measurement with those of alveolar gas uniformity[6] (single breath oxygen and nitrogen washout) measurements, physiological dead space, and hematocrit, considerable insight is gained with respect to the most likely pathophysiological state which might account for the reduction in CO uptake.

Because the values for the diffusing capacity of the lung for carbon monoxide (DL) for normal subjects at extreme ranges in age are scanty in the literature, we made measurements of DL and the rate of CO transfer per unit of alveolar volume (DL/VA) on 82 normal subjects between ages 5 and 76. Regression equations have been calculated. We find that for the extremes of ages, the normal values presented here are more representative than that in the literature. However, for subjects between 20 and 50 years old, there is little difference between our results and those in the literature. The purpose of this paper is to provide normal values for DL and DL/VA by the single breath technique in children and adults and to illustrate the use of the measurement of DL/VA to evaluate the physiological basis of a reduced DL.

Theoretical Considerations

The pathophysiologic entities which can account for reductions in DL are described in Figure 1. A reduced DL can occur with a proportional reduction in alveolar volume (normal DL/VA) or with no reduction in alveolar volume (↓DL/VA).

A reduced DL, but normal DL/VA must be explained either by failure of the inspired gas to reach all of the normal diffusing membranes (Factor I, maldistribution of ventilation) or by

loss of lung units (Factor II, parenchymal fibrosis, or partial lung resection). In the case of Factor I, results of tests of distribution of ventilation would be abnormal, especially the single breath oxygen test (Comroe and Fowler). Also, in most cases, the alveolar volume would be less than 80 percent of the patient's actual total lung capacity. In the case of Factor II, the distribution of ventilation might be normal and the alveolar volume would usually be less than 80 percent of predicted total lung capacity.

Pathophysiological states in which DL and DL/VA are reduced fall into four categories. Commonly, patients with emphysema (Factor III) have enlarged alveolar spaces which receive part of the inspired gas during the single breath CO uptake test. Since the volume increases in the enlarged alveolar spaces as the cube of the radius while the surface area increases as the square of the radius (DL will be directly proportional to surface area), the ratio of DL to alveolar volume will decrease as the radius of the alveolus increases. A reduction of vascular supply to the emphysematous units without a comparable loss in ventilation will also result in a decrease in DL and DL/VA.

The rate-limiting factor in the uptake of CO by the blood is the number of red blood cells (hemoglobin) present in each milliliter of blood in the functioning pulmonary capillaries. The greater the number of red blood cells available per milliliter of blood, the less the time for CO molecules to encounter a red blood cell and be removed from its dissolved gaseous state. In anemia, (Factor IV) CO uptake is reduced because fewer red blood cells are present in each milliliter of blood and therefore diffusion distances in the liquid phase are increased. As a re-

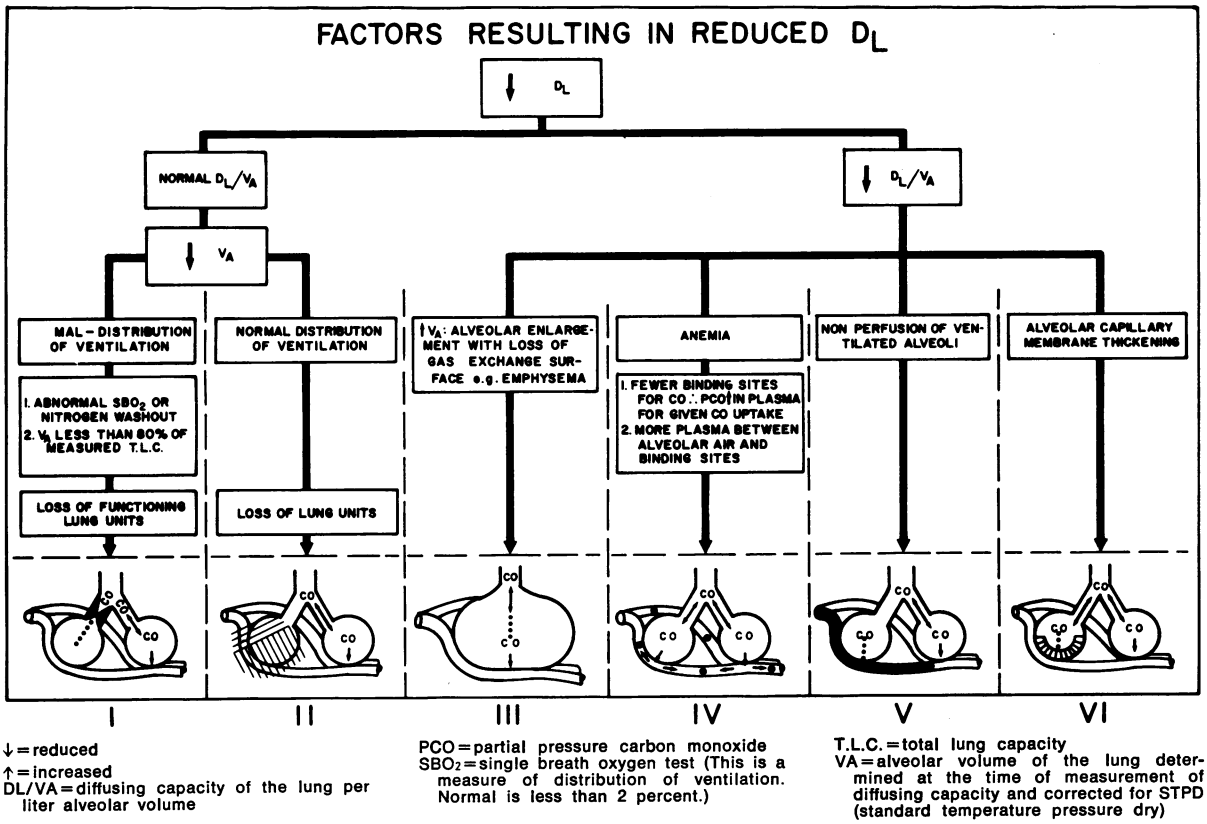

Figure 1.—Schema illustrating the causes of a reduced diffusing capacity of the lung for carbon monoxide (DL). Factor I: failure of inspired gas to reach alveoli (maldistribution of ventilation); Factor II: loss of alveoli as a result of fibrosis and scarring of the entire gas exchange unit or lung resection; Factor III: enlarged alveolar spaces with reduction in gas exchange surface (emphysema); Factor IV: a deficiency in red blood cells increasing the intravascular diffusion distance (anemia or abnormal hemoglobin); Factor V: loss of pulmonary capillary bed (thromboembolism or vasculitis); Factor VI: increase of the distance between the gas and blood phase of the functional lung unit due to filling of the alveolar-capillary membrane resulting from interstitial fibrosis, inflammation or edema.

TABLE 1.—*Age and Sex Distribution of Subjects Used in This Study*

	Age		Number of Subjects Male	Female
Normal				
Group 1	5-17	.....	12	9
Group 2	18-45	.....	22	10
Group 3	46-76	.....	15	14
Patients				
Group 1	20-50	Lymphoma treated with radiation ...	5	0
Group 2	23-74	Various pulmonary diseases	14	10

sult of the increased diffusion path due to anemia, the partial pressure of CO will increase in plasma and result in a decreased pressure gradient for CO transfer from the alveolar gas to the lung capillary. The presence of anemia can be easily determined and a correction can be made for this as described by Staub and co-workers.[23]

Vascular obstruction of aerated areas of the lungs (Factor V) decreases pulmonary capillary blood volume. Ventilation of these poorly perfused areas results in an increase in physiological dead space (wasted ventilation) and arterial-end tidal carbon dioxide (CO_2) differences. These abnormal physiological measurements can help separate this cause of a reduced DL from others.

Increased distance between capillary blood and alveolar gas space (Factor VI) could account for a reduction in DL/VA as well as DL during the standard single breath CO-diffusing capacity test. A classic example of reduced DL due to increased diffusion distance is alveolar proteinosis. In this condition, CO diffusion is reduced by a barrier of proteinaceous material which fills the alveolus

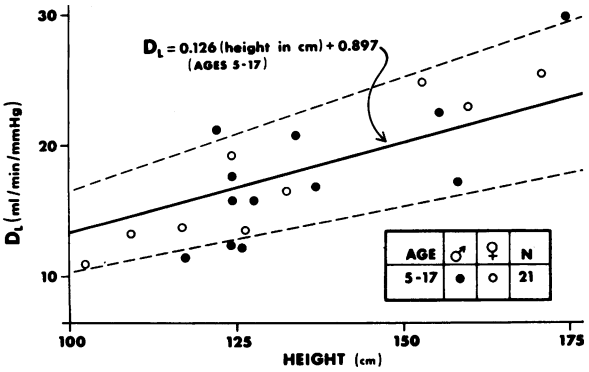

Figure 2A.—The relationship of diffusing capacity of the lung for carbon monoxide (DL) to height of normal children ages 5 through 17. Dashed lines are ± 25 percent of the points from the mean regression line. Correlation coefficient=.46; coefficient of variation=15 percent.

and respiratory bronchioles. However, the physiological dead space and arterial-end tidal CO_2 differences are normal and reflect the normal vascular supply to the alveoli and the high solubility of CO_2 in the alveolar material.

Methods

The CO diffusion capacity was measured by the single breath method.[11,19] The gas composition was 25.0 percent oxygen, 0.35 percent CO, 0.6 percent neon and the balance nitrogen. All samples of expired gas were analyzed with a gas chromatograph (Microtek, Tracor, or Hewlett-Packard).

To determine normal values for DL and DL/VA, 82 normal subjects were studied ranging in age from 5 to 76 years (Table 1). The subjects consisted of referrals undergoing pulmonary function studies as part of an annual or initial physical examination, hospital employees and family members of hospital employees. Selection criteria included no history of cardiopulmonary disease, no respiratory complaints, no anemia, normal vital capacity and forced vital capacity. Twenty percent of the subjects were smokers or ex-smokers of cigarettes.

Two groups of patients were studied, one consisting of five subjects with lymphoma before and after undergoing radiation therapy to the mediastinum and a second group of 24 patients with a variety of pulmonary pathological lesions (Table 1).

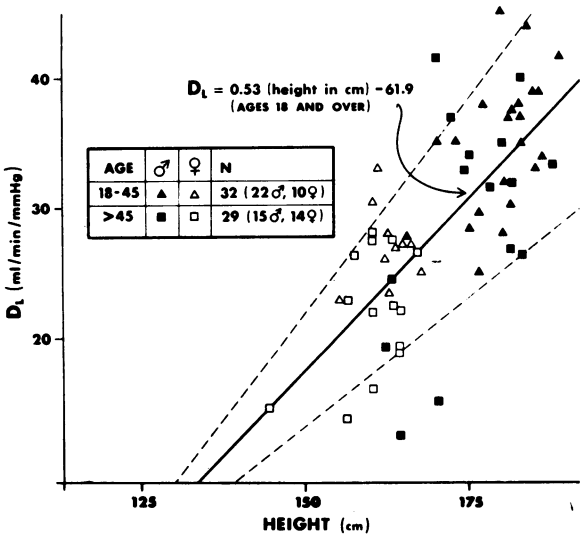

Figure 2B.—The relationship of DL to height of normal adults ages 18 through 76. Dashed lines are ± 25 percent of the points from the mean regression line. Correlation coefficient=.72; coefficient of variation=6 percent.

Results

Figures 2A and 2B show the relationship between DL and height in normal subjects ages 5 through 76. This relationship is not a linear one. Linear regression curves can be fitted to the data for children ages 5 through 17 (Figure 2A) and adults ages 18 through 76 (Figure 2B). In both sets of data, DL is independent of age and sex.

Figures 3A and 3B relate DL observed in our normal subjects over 50 years of age with the DL predicted from the literature[17] and from the regression equation of our normal adults over 18 years of age respectively. In Figure 3A, values in 17 of 26 persons are above 120 percent and in 1 of 26 below 75 percent of the literature's predicted DL. In Figure 3B, values in 4 of 26 are above 120 percent and in 4 of 26 are below 75 percent of the new predicted DL. Figure 3A shows that use of the constant reduction of 3 ml of CO per minute per mm of mercury for every 10 years increase in age will significantly underestimate DL in most patients over 50 years of age.

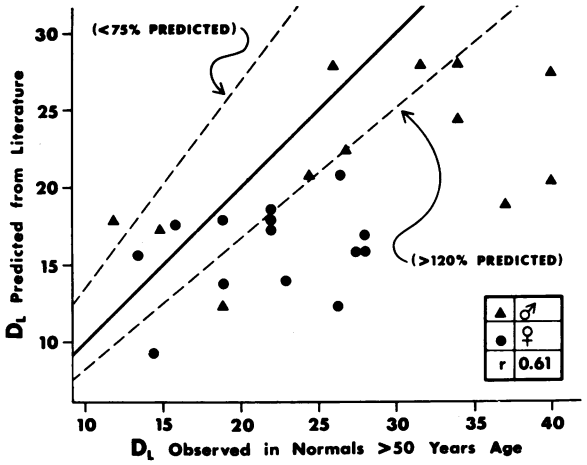

Figure 3A.—The relationship of observed diffusing capacity of the lung for carbon monoxide (DL) in normal adults over 50 years of age with DL predicted from data of McGrath and Thompson.[17] Dashed lines are less than 75 percent and more than 120 percent of the predicted DL.

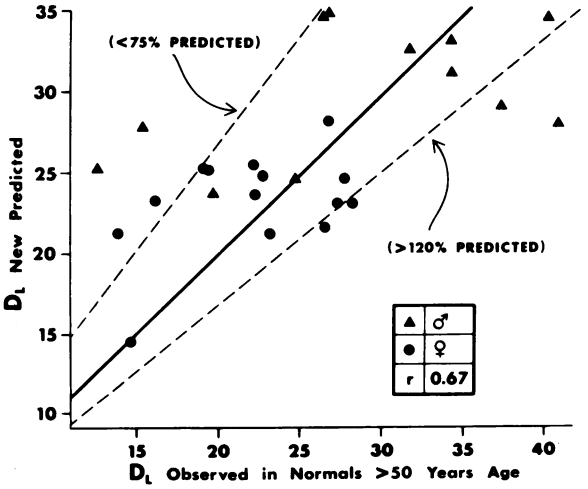

Figure 3B.—The relationship of observed DL in normal adults over 50 years of age with DL predicted from Figure 2B for adults (DL=0.53 [height in cm]—61.9). Dashed lines are less than 75 percent and more than 120 percent of the predicted DL.

Figure 4 shows the relationship between DL/VA (ratio of lung diffusing capacity to alveolar lung volume at the time of measurement as estimated by dilution of the inert gas in the test gas mixture) and height in normal subjects ages 5 through 76. This relationship is linear on an arithmetic plot and is unrelated to the age and sex of the subject. When expressed as DL/VA, the 5 to 17 year age group relates to height in the same way as adults. In contrast to DL, DL/VA decreases with height. This observation is compatible with the concept of the growth of alveoli rather than the increase in number of alveoli associated with the growth of the subject. Therefore, the ratio of surface area for absorption relative to the volume from which the gas is absorbed will decrease since the surface to volume ratio decreases with growth.

Patient Studies: Application and Interpretation

Interpretation of the DL/VA measurement is only indicated in the evaluation of a reduced DL. One can appreciate that hyperinflation (increased VA) with a normal pulmonary capillary bed (nor-

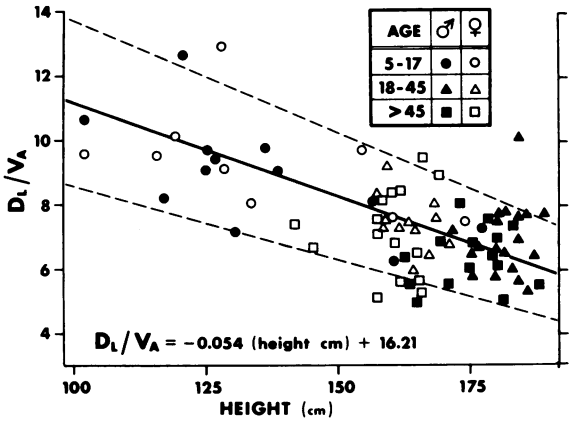

Figure 4.—The linear relationship of diffusing capacity of the lung per liter alveolar volume (DL/VA) to height. Dashed lines are ± 25 percent of the points from the mean regression line.

mal DL) will result in a reduced DL/VA. Also, poor subject cooperation during the DL measurement will result in underestimation of VA, normal DL and increased DL/VA.

Figure 5 shows the results of serial DL measurements on a group of five patients having radiation therapy for lymphoma. There is a sharp fall in DL within three months of irradiation. In contrast to the reduction in DL there is a lesser decrease in specific diffusing capacity (DL/VA), the reduction being within 75 percent of the control values in four subjects. This suggests that the reduction in DL is due mainly to a loss of lung units (alveoli and capillaries) rather than alveolar capillary membrane thickening (interstitial disease) as a major factor in the reduction of DL.

The effect of disease on DL and DL/VA is illustrated in Table 2. In *Cases 13, 17, 18, 20, 23 and 24* a reduction in DL is shown with an equal reduction in VA resulting in a normal specific diffusing capacity, while in *Cases 1 through 4 and 9 through 12* there is primarily reduction in DL without reduction in VA causing DL/VA to be reduced. The patients in whom DL/VA is reduced are primarily those patients with pulmonary vascular occlusive disease or emphysema.

Longitudinal studies in five patients representing four types of pathophysiology are illustrated in Table 3. The predicted values for DL/VA were obtained from Figure 4. In *Case 22* there was an increased alveolar-arterial (A-a) oxygen difference as well as low DL/VA in the early part of the patient's course. Since anemia (Factor IV) was not present, Factor V and Factor VI remain as the most likely causes of the reduced DL/VA in the patient (Figure 1). Subsequently, the patient's vital capacity and DL/VA improved slightly, while the alveolar-arterial oxygen difference improved to a much greater degree. We have commonly noted this as a disease goes from an acute or subacute to a chronic stage. A possible reason for the more striking improvements in the A-a oxygen difference than in DL is that the perfusion shifts as the inflamed lung units scar. Thus, DL would remain decreased since transfer of CO would be impaired whether the diseased lung unit was inflamed or scarred. However, the hypoxia would disappear as perfusion shifts in the conversion of inflammation to fibrosis.

Case 24 in Table 3 illustrates the course of a patient with Histiocytosis X lung disease. Various doses of steroids had been given throughout the course. DL/VA remained normal despite the abnormal alveolar-arterial oxygen differences and the low DL values. The severe abnormality in distribution of ventilation in this patient (Table 2) and the loss of lung units by scarring are most likely responsible for the reduction in DL. The

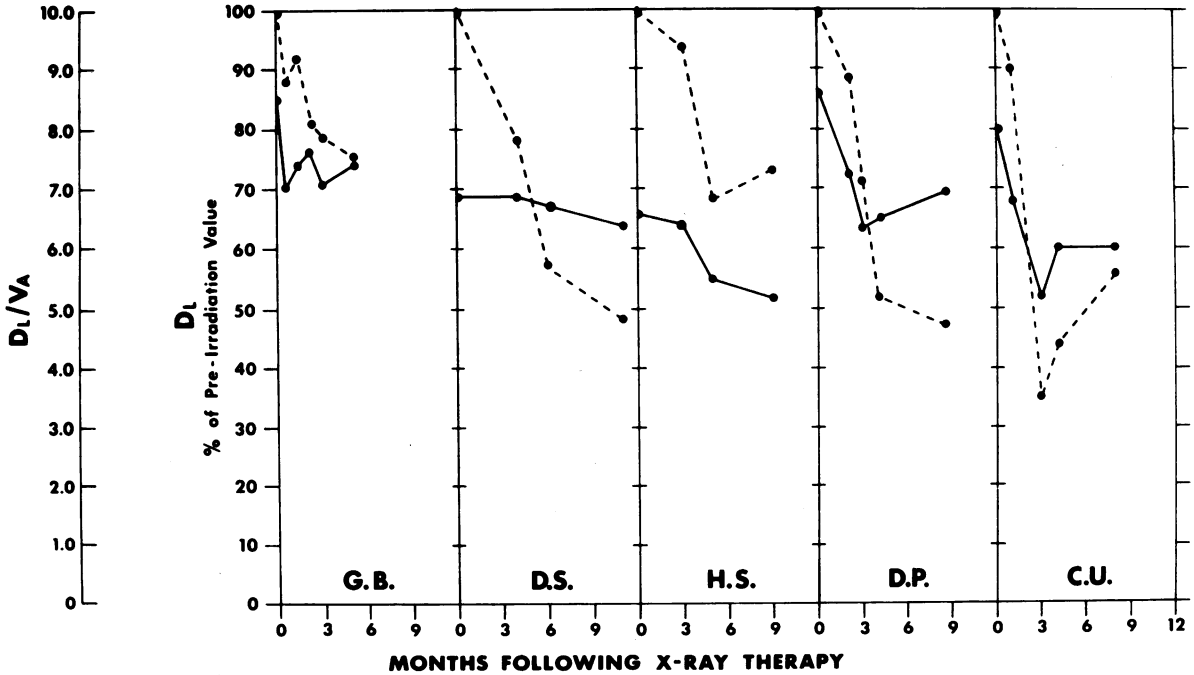

Figure 5.—Effect of radiotherapy on diffusing capacity (DL) and specific diffusing capacity (DL/VA) in five patients. DL is in solid lines and is represented as percent of pre-irradiation value while DL/VA is in dashed lines and is represented as diffusion per liter alveolar volume.

variable alveolar-arterial oxygen differences were correlated with periods of clinical improvement and exacerbation. Again, the persistently low DL values and near-normal DL/VA values are likely the result of scarring of lung units, (Factor I or Factor II) both vessels and alveoli.

Case 13 in Table 3 represents one type of pathophysiological defect which can occur in pulmonary alveolar proteinosis. In this patient, there was a pronounced reduction in vital capacity as well as a reduced DL. The DL/VA was within normal limits. The alveolar-arterial oxygen difference was moderately severely increased. This pathophysiological pattern suggests that those alveoli which are functioning, are able to absorb CO relatively normally. However, there had been a severe loss of functional lung units in the patient as evidenced by the reduced DL. Those that are not functioning are apparently filled with proteinaceous material which is equivalent to loss of lung units (Factor II). Perfusion apparently persists to a certain degree accounting for the increased alveolar-arterial oxygen differences. Findings on a biopsy study of the lungs confirm that the respiratory units from the alveolar membrane to the terminal bronchioles can be completely filled with the amorphous material characteristic of pulmonary alveolar proteinosis.

Case 14 (Table 3) is an example of the same disease but with somewhat different pathophysiology. There is apparently little loss in functional lung units since the vital capacity is normal. However, the DL/VA is reduced, suggesting that the proteinaceous material in the alveoli is inhibiting diffusion but not completely filling the functional lung unit (Factor V or VI). Treatment results in

TABLE 2.—*Effect of Disease on DL and DL/VA*

Case	Sex, Height (cm), Age	Maximum Expiratory Flow Rate (Normal over 300 L/min)	Single Breath Oxygen (Normal less than 2%)	Seven Minute Nitrogen Washout (Normal less than 2%)	DL mlCO/ mmHg/min	Percent Predic.	DL/VA mlCO/ mmHg/min/L	Percent Predic.	Basis of Diagnosis*
EMPHYSEMA									
1	... ♂ 170.0 69	88	4.1	3.75	15.5	57	2.7	39.0	1,2,4
2	... ♂ 170.0 60	36	10.5	8.0	9.2	34	2.1	30.0	1,2,4,6
3	... ♂ 185.5 48	18	..	..	3.8	10	1.6	26.0	1,2,4
4	... ♀ 181.5 61	49	10.1	7.1	16.2	49	3.8	59.0	1,2,4
BRONCHIAL ASTHMA									
5	... ♂ 154.0 22	157	4.5	4.5	33.2	166	8.8	144.0	1,2,4
6	... ♀ 162.0 66	272	2.5	0.7	19.3	80	4.48	90.0	1,2,4
7	... ♂ 181.0 36	187	2.2	1.2	33.1	100	6.9	121.0	1,2,4
8	... ♀ 142.0 17	120	2.3	0.49	19.5	149	7.6	96.0	1,2,4
PULMONARY EMBOLI									
9	... ♀ 167.5 42	240	4.3	0.50	12.2	45	3.1	44.0	1,2,3,4,7
10	... ♂ 173.0 74	385	..	0.25	14.0	47	3.2	48.0	1,2,3,4,7
11	... ♂ 167.5 53	213	..	0.65	9.9	37	2.0	29.0	1,2,3,4,7,8
12	... ♂ 172.0 61	333	4.5	0.78	11.3	39	2.0	39.5	1,2,3,4,7
PULMONARY ALVEOLAR PROTEINOSIS									
13	... ♀ 160.0 23	320	1.0	0.5	7.4	31	6.2	83.0	1,5
14	... ♀ 165.0 42	..	6.0	0.85	8.2	31	3.1	43.0	1,5
15	... ♂ 179.0 34	384	2.0	0.5	19.4	61	6.6	67.0	1,5
16	... ♂ 184.0 26	428	3.3	0.4	10.3	29	7.1	48.0	1,5
SARCOIDOSIS									
17	... ♀ 160.0 38	300	1.0	0.7	16.7	70	6.88	89.0	1,4
18	... ♀ 165.0 60	160	5.5	0.5	9.2	35	4.8	90.5	1,3,4
19	... ♂ 176.0 38	91	6.5	0.4	22.4	72	8.8	144.0	1,3,4
20	... ♂ 180.0 25	300	4.0	0.4	17.3	52	5.8	100.0	1,3,4
MISCELLANEOUS INTERSTITIAL FIBROSIS									
21	... ♂ 173.0 63	320	9.0	0.4	10.9	36	4.8	70.0	1,2,3,4
22	... ♀ 158.5 18	240	..	0.55	6.7	29	4.3	57.0	1,4,5
23	... ♂ 188.0 46	375	1.36	0.79	12.2	33	5.59	108.0	1,2,3,4
24	... ♀ 183.0 31	31	7.7	7.3	11.4	33	5.2	84.0	1,5

*1=X-ray; 2=History and physical; 3=Clinical course; 4=Respiratory function testing; 5=Lung biopsy; 6=Postmortem; 7=Lung scan; 8=Cardiac catheterization.

DL=diffusing capacity of lung for carbon monoxide

DL/VA=diffusing capacity of lung for carbon monoxide per liter alveolar volume

improvement of both DL and DL/VA as well as arterial oxygenation.

The course and response to lung lavage in another patient with alveolar proteinosis is described in *Case 16* (Table 3). The pronounced reduction in diffusing capacity and in DL/VA is compatible with many lung units which are partially filled and functioning (Factor V or VI). Lung lavage results in removal of this proteinaceous material and consequently an increase in DL and DL/VA and reduction in the large alveolar-arterial oxygen difference.

Cases 1 through 4 (Table 2) illustrate characteristic findings in emphysema. Severe maldistribution of ventilation accompanies this disease. Reduction in DL/VA suggests that the reduced DL is due to a decreased capillary bed or enlargement of the alveolar spaces or both, and is not due solely to maldistribution of inspired carbon monoxide.

In asthma (*Cases 5 through 8,* Table 2), normal diffusing capacity and DL/VA are found. The observation of normal diffusion in obstructive airway diseases is compatible with a normal intact pulmonary capillary bed and contrast with the findings in emphysema.

Cases 9 through 12 (Table 2) are representative of multiple small pulmonary emboli and illustrate a very low specific diffusing capacity (DL/VA). Excluding ventilation abnormalities the factors that determine DL in the presence of pulmonary vascular obstruction are size of pulmonary vessels obstructed, presence or absence of bronchial collateral blood flow and location of emboli within the different zones of vascular perfusion in the lung.[25] Thus if the emboli are in larger vessels and the capillaries are open and contain red blood cells, DL will not be affected but if pulmonary capillaries are obstructed DL must decrease.

Cases 17 through 20 (Table 2) show that reduction in diffusing capacity with sarcoidosis is associated with loss of alveolar units and a relatively normal specific diffusing capacity. Could this reduction in DL merely reflect a reduction in alveolar volume without a loss of capillary bed? Against this argument are the observations by Miller and Johnson that in normal subjects DL is reduced from 0 to 12 percent when determined at half of total lung capacity.[26] The reduction of DL in *cases 17 through 20* is far greater than could be accounted for by low lung volumes alone and loss of alveolar units, both capillaries and alveoli, has occurred and resulted in the relatively normal specific diffusing capacity.

Cases of idiopathic interstitial fibrosis, (*cases 21 through 24,* Table 2) are most commonly associated with a reduced DL and alveolar volume. Therefore, DL/VA is commonly normal, but might be reduced to a lesser degree than DL.

TABLE 3.—*Abnormal Diffusing Capacity Measurements*

Date	Percent of Predict. V.C.	DL mlCO/ mmHg/ min.	DL Percent Predict.	DL/VA mlCO/ mmHg/ min/L	DL/VA Percent Predict.	Alveolar-Arterial O_2 Difference* mmHg
CASE 22 Diffuse Interstitial Fibrosis Height (cm)=158.5						
9-26-67	29	6.7	29	4.3	57	50
10-10-67	34	5.6	24	3.6	48	45
11-7-67	40	7.6	33	4.8	63	26
11-27-67	49	9.0	39	5.7	75	24
12-19-67	55	9.4	41	5.8	77	27
1-11-68	60	8.8	38	4.5	60	..
2-1-68	59	8.6	37	4.4	58	25
CASE 24 Histiocytosis X Lung Disease Height (cm)=183						
7-18-67	..	..	..	..	..	50
7-24-67	..	..	..	..	..	29
8-7-67	..	..	..	..	..	21
10-25-67	38	11.4	33	5.2	84	28
11-30-67	41	9.3	27	5.0	80	33
12-22-67	45	..	..	..	..	52
11-25-68	41	12.2	35	5.2	84	33
CASE 13 Pulmonary Alveolar Proteinosis Height (cm)=160						
10-23-67	22	7.4	31	6.0	82	64
10-30-67	Left lung lavage					51
11-3-67	29	8.3	35	5.5	74	66
11-6-67	Right lung lavage					
11-9-67	44	12.0	50	6.8	92	21
11-21-67	..	9.4	39	5.5	74	..
2-6-68	62	13.6	57	6.8	92	24
CASE 14 Pulmonary Alveolar Proteinosis Height (cm)=165						
6-2-66	96	8.2	32	3.1	43	70
6-13-66	Left lung lavage					
6-15-66	..	11.2	43	3.9	54	54
6-17-66	Right lung lavage					
6-20-66	104	14.0	54	4.1	58	35
9-8-66	116	19.6	82	5.1	71	10
CASE 16 Pulmonary Alveolar Proteinosis Height (cm)=184						
5-1-73	63	10.3	29	3.4	48	54
5-3-73	Left lung lavage					
5-4-73	78	15.1	42	4.4	62	37
5-7-73	Right lung lavage					
5-8-73	80	20.2	56	5.5	78	24

*Normal alveolar-arterial O_2 difference <20 mmHg (Air-breathing at sea level).
VC=vital capacity
DL=diffusing capacity of the lung for carbon monoxide
DL/VA=diffusing capacity of lung for carbon monoxide per liter alveolar volume

Discussion

The diffusing capacity is a measure of the pathophysiology of the pulmonary disease process. One purpose of the paper is to point out the many factors which might cause the diffusing

capacity (DL) to be abnormal. A reduced DL may be present because of a loss of pulmonary capillaries to ventilated lung, anemia, alveolar-capillary membrane thickening or uneven distribution of ventilation.[2,13,14,17]

In this paper, we examine both DL and DL/VA as related to the simultaneously measured alveolar volume (specific diffusing capacity) in normal subjects and patients.

The relationship of diffusing capacity (DL) to lung volume in any given subject was first pointed out by Marie Krogh in 1915.[13] She noted that DL was constant below a lung volume which she called the mean capacity. Above this lung volume, DL increased. She thought that this was due to thinning of the alveolar-capillary membrane and consequently a shorter diffusion path as the alveoli enlarged.

In order to standardize the measurement of DL for clinical purposes, corrections in DL have been made with age, height, body surface area, sex and alveolar volume.[4,7,17] However, the scatter in these correlations is wide. In general, we find that the predictive values in the literature are underestimates for patients over the age of 55 years. Measurements in children are difficult to find.

McGrath and Thompson related their measurements to height and age in adults.[17] As expected, DL increases with height. However, we find that the use of a constant reduction of 3 ml of CO per minute per mm of mercury for each 10 years of adult aging as used by these investigators is not consistent with observations. It results in extremely low and unrealistic predicted values for elderly patients. Perhaps their older population was also a shorter population in height, thereby making a spurious negative correlation with age.

McGrath and Thompson[17] found that DL in women of a given height and age was 10 percent less than in men. However, Burrows and coworkers[4] found no relationship between DL and sex. The difference in the observation of these authors might be due to the lack of sufficient uniformity in the DL measurement in a given population. A 10 percent difference is probably just outside of the experimental error of measurement. We do not find statistical differences in DL in the two sexes when the values measured are related to height.

Teculescu and Stanescu found that DL in men was lower in smokers.[27] Although smoking appears to be a significant factor in a reduced DL only 20 percent of our adult subjects were smokers or exsmokers. Also the scatter of DL with height was less in our normal subjects (coefficient of variation = 6 percent) when compared with the regression equation of Teculescu and Stanescu[27] which plotted DL with height and age (coefficient of variation = 14.1 percent).

Our studies include measurements in normal children and normal adults taken from Harbor General Hospital and Stanford Medical Center and represent a wider age group than previously studied. In children ages 5 to 17 years and adults 18 to 76 years, DL is linearly related to height. Eighty-seven percent of the adults fall within ±25 percent of the predicted, whereas 76 percent of the children fall within ±25 percent of the predicted range. When Burrows and co-workers[4] established regression relationships with age and concluded that DL decreased with age, the scatter of their data was wide and the height factor was not standardized. There is a tendency for young adults to be taller than elderly adults.

Both in children and adults DL/VA is linearly related to height but unrelated to age (Figure 3). The average values for DL/VA in our studies closely agree with those of Burrows and associates.[4] However, their data show greater scatter than our own, probably because they standardized against age while we correlated our data to height.

Our data (Figure 4) demonstrate that the relationship of DL/VA and height correlated for pediatric as well as adult patients and is unrelated to the age and sex of the subject. The smaller the subject, the greater is the volume of CO extracted from each liter of alveolar volume. DL/VA of 5 was the lowest value obtained in our tallest subjects while 13.6 was the highest seen in our smallest subjects.

The significance of the relationship of DL to height might be that smaller subjects have smaller alveoli and therefore more surface area per liter of alveolar volume. Therefore, more CO could be absorbed since the absorbing surface per liter of alveolar volume would be greater than that for taller subjects. Since the total number of alveoli remains constant after age seven,[8,24] the subsequent enlarging alveolar volume during growth increases as the cube of the radius while the surface area only increases as the square of the radius. Thus, alveolar volume would increase with growth out of proportion to absorbing surface.

We feel that the specific diffusing capacity or

the CO extracted per liter of alveolar volume (DL/VA) is useful for gaining a better understanding of the pathophysiology associated with a reduced DL.

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